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DATE: Friday, August 15, 2003

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,DWPI; PLUR=YES; OP=ADJ		
L5	nickoloff-brian$.in. or miele-lucio$.in.	8	L5
L4	L1 same (epitheil$ or keratinocyt$ or epiderm)	3	L4
L3	L1 and (epitheil$ or keratinocyt$ or epiderm)	11	L3
L2	L1 same3 (epitheil$ or keratinocyt$ or epiderm)	0	L2
L1	jagged-1 or jagged1 or jag-1 or jag1 or (jagged adj 1)	37	L1

END OF SEARCH HISTORY

ID ABB07829 standard; Protein; 21 AA.
XX
AC ABB07829;
XX
DT 03-JUL-2002 (first entry)
XX
DE Human jagged 1 (JAG-1c) notch ligand.
XX
KW Cell differentiation; notch; epidermis; cytostatic; dermatological;
KW epithelial; skin; cancer; gamma secretase; human; jagged protein.
XX
OS Homo sapiens.
XX
PN WO200218544-A2.
XX
PD 07-MAR-2002.
XX
PF 31-AUG-2001; 2001WO-US27246.
XX
PR 31-AUG-2000; 2000US-229614P.
XX
PA (LOYO) UNIV LOYOLA CHICAGO.
XX
PI Nickoloff BJ, Miele L;
XX
DR WPI; 2002-339659/37.
XX
PT Inducing differentiation of epithelial cell useful for inducing barrier
PT formation within epithelium for treating psoriasis, sunburn, involves
PT exogenously providing a source of a Notch agonist to the epithelial
PT cell -
XX
PS Claim 10; Page 95; 101pp; English.
XX
CC The invention relates to a method of inducing differentiation of
CC at least one epithelial cell. The method involves exogenously providing
CC at least one source of at least one Notch agonist to at least one
CC epithelial cell, whereby the Notch pathway is activated within at least
CC one epithelial cell so that the differentiation of the cell is induced.
CC Methods of producing differentiated epidermis; for assaying for genetic
CC propensity of a patient to develop a disorder associated with epithelial
CC barrier formation; for retarding progression of skin cancer and for
CC diagnosing aggressive melanoma are also provided. The methods are useful
CC for inducing differentiation of at least one epithelial cell e.g. a
CC keratinocyte or a pre-malignant cell, in vivo or ex vivo. The method is
CC useful for inducing differentiation of epithelial cell within cutaneous
CC epithelial tissue or dermal equivalent, or within extracutaneous
CC epithelium such as oral mucosal epithelial tissue, cornea epithelial
CC tissue, gastrointestinal epithelia, urogenital epithelia, or respiratory
CC epithelia. The methods are useful retarding the progression of skin
CC cancer such as aggressive melanoma, aggressive cutaneous T-cell lymphoma
CC (CTCL), aggressive squamous cell carcinoma, or aggressive basal cell
CC carcinoma, by preferably administering an antagonist of the Notch
CC pathway such as gamma secretase inhibitor. The present sequence
CC represents a human jagged 1 (JAG-1c) notch ligand.
XX
SQ Sequence 21 AA;

Query Match 100.0%; Score 123; DB 23; Length 21;
Best Local Similarity 100.0%; Pred. No. 1.3e-11;
Matches 21; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 ADDYYYGFGANKFGRPRDDFF 21
              |||||||||||||||||||||
Db          1 ADDYYYGFGANKFGRPRDDFF 21
```

JAG1_HUMAN
ID   JAG1_HUMAN   STANDARD;   PRT; 1218 AA.
AC   P78504; O15122; O14902; Q15816;
DT   15-JUN-2002 (Rel. 41, Created)
DT   15-JUN-2002 (Rel. 41, Last sequence update)
DT   15-JUN-2002 (Rel. 41, Last annotation update)
DE   Jagged 1 precursor (Jagged1) (hJ1).
GN   JAG1.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
  Query Match   86.2%; Score 106; DB 1; Length 1218;
  Best Local Similarity   90.0%; Pred. No. 9.7e-09;
  Matches   18; Conservative   0; Mismatches   2; Indels   0; Gaps   0;

Qy   2 DDYYYGFGANKFGRPRDDFF 21
              |||||||| ||| |||||||
Db   188 DDYYYGFGCNKFCRPRDDFF 207

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=> d his

     (FILE 'HOME' ENTERED AT 10:04:37 ON 15 AUG 2003)

     FILE 'MEDLINE, EMBASE, CAPLUS' ENTERED AT 10:04:51 ON 15 AUG 2003
L1           520 S JAGGED1 OR JAGGED-1 OR JAG1 OR JAG-1 OR HJAGGED1 OR HJAGGED-1
L2           149 S L1 AND (EPITHELI? OR KERATINOCYT? OR EPIDERM?)
L3            76 DUP REM L2 (73 DUPLICATES REMOVED)
L4            90 S SERRATE?(10A)(EPITHELI? OR EPIDERM?)
L5            47 DUP REM L4 (43 DUPLICATES REMOVED)

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L3 ANSWER 54 OF 76 MEDLINE on STN DUPLICATE 29
TI **JAGGED1** gene expression during human embryogenesis elucidates the wide phenotypic spectrum of Alagille syndrome.
AU Crosnier C; Attie-Bitach T; Encha-Razavi F; Audollent S; Soudy F; Hadchouel M; Meunier-Rotival M; Vekemans M
SO HEPATOLOGY, (2000 Sep) 32 (3) 574-81.
Journal code: 8302946. ISSN: 0270-9139.
AB Mutations of the **JAGGED1** gene, encoding a NOTCH receptor ligand, cause Alagille syndrome (AGS), a complex malformative disorder affecting mainly the liver, heart, vertebrae, eye, and face. Minor and occasional features involving kidney, pharynx, systemic arteries, skeleton, and ear are in some cases associated with the syndrome. To describe the expression of **JAGGED1** during human embryogenesis and to study its relationship with all the features of AGS, we performed in situ hybridization studies on human embryos and fetal tissue sections. **JAGGED1** was mainly expressed in the cardiovascular system. In the liver, **JAGGED1** transcripts were only detected in blood vessels. **JAGGED1** was also expressed in other structures of mesenchymal origin (distal mesenchyme of limb buds; mesonephric and metanephric tubules of the kidney) and in **epithelial** structures including the ciliary margin of the retina and the posterior part of the lens, the ventral **epithelium** of the otic vesicle, the neurosensory **epithelium** of the ear vestibule, the **epithelium** of pharyngeal arches, and the developing central nervous system. The strong **JAGGED1** expression during human embryo- and feto-genesis both in the vascular system and in other mesenchymal and **epithelial** tissues implicates abnormal angiogenesis in the pathogenesis of Alagille syndrome and particularly the paucity of interlobular bile ducts. However, it is probably not the only mechanism of the disease. Except for the central nervous system, there is a strong correlation between **JAGGED1** expression and all the features of AGS. This implies that the features occasionally associated with the syndrome are not coincidental.

L3 ANSWER 67 OF 76 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN
TI Mutation analysis of a family with Alagille syndrome.
AU Satoh H.; Okada T.; Sawada T.; Takeda Y.; Mabuchi H.; Kitoh C.; Tatsumi Y.; Shiono Y.; Azuma T.
SO Japanese Pharmacology and Therapeutics, (1999) 27/SUPPL. 3 (123-126).
Refs: 10
ISSN: 0386-3603 CODEN: YACHDS
AB Alagille syndrome is an autosomal dominant inherited disorder characterized by cholestasis due to intrahepatic bile duct paucity in combination with heart, skeletal, ocular, renal involvement and characteristic facial features. We performed mutation analysis to a family with Alagille syndrome. The proband was 27 years-old female and was diagnosed as Alagille syndrome at 13 years of age. She had histologically proved intrahepatic bile duct paucity, characteristic face, butterfly vertebrae, chronic renal failure. **Jagged-1** gene was studied by SSCP and direct sequencing then revealed a novel mutation 2556ins GTGC. Her mother and brother had same mutation and they were considered Alagille syndrome. This mutation leads to a translational frameshift and produces a truncated protein with an altered codon 715 and a premature stop codon in the EGF-like repeats domain of **JAG-1**. Analyzing previously reported cases, it seems that mutations in the EGF-like repeats are closely related with renal manifestations in Alagille syndrome. The fact that all of the family members have renal manifestations may support the hypothesis.

L3 ANSWER 58 OF 76 MEDLINE on STN DUPLICATE 30
TI The role of the **epidermal** growth factor-like protein dlk in cell

differentiation.

AU Laborda J

SO HISTOLOGY AND HISTOPATHOLOGY, (2000 Jan) 15 (1) 119-29. Ref: 40
Journal code: 8609357. ISSN: 0213-3911.

AB This review focuses on the current knowledge about the function of the EGF-like homeotic protein dlk. dlk is a transmembrane protein that possesses six **Epidermal** Growth Factor-like sequences at the extracellular domain, a single transmembrane domain and a short intracellular tail. Because of its overall structure and amino acid homology, dlk belongs to the EGF-like homeotic protein family. This family includes proteins such as the Notch receptor and its homologues, as well as Notch ligands, such as Delta, Serrate, and their mammalian homologues Dll1, Dll2 and Dll3 and **Jagged 1** and Jagged 2. (For a recent review see Fleming, 1998). dlk is highly expressed by preadipose cell lines, and neuroendocrine tumors, such as pheochromocytomas and neuroblastomas. dlk has been involved in several differentiation processes, such as adipogenesis, hematopoiesis and B cell lymphopoiesis, and neuroendocrine differentiation, including the differentiation of pancreas and the adrenal gland. The extracellular region of dlk can be released by action of an unknown protease and this soluble dlk variant accumulates in the amniotic fluid and is able to inhibit adipocyte differentiation in vitro. Recent evidence indicates, however, that membrane-associated dlk variants play a positive role in the differentiation process. These findings suggest that dlk plays an important role in differentiation and tumorigenesis of several cellular types.

L3 ANSWER 50 OF 76 MEDLINE on STN DUPLICATE 26

TI Familial Tetralogy of Fallot caused by mutation in the **jagged1** gene.

AU Eldadah Z A; Hamosh A; Biery N J; Montgomery R A; Duke M; Elkins R; Dietz H C

SO HUMAN MOLECULAR GENETICS, (2001 Jan 15) 10 (2) 163-9.
Journal code: 9208958. ISSN: 0964-6906.

AB Tetralogy of Fallot (ToF) is the most common form of complex congenital heart disease, occurring in approximately 1 in 3000 live births. Evaluation of candidate loci in a large kindred segregating autosomal dominant ToF with reduced penetrance culminated in identification of a missense mutation (G274D) in **JAG1**, the gene encoding **jagged1**, a Notch ligand expressed in the developing right heart. Nine of eleven mutation carriers manifested cardiac disease, including classic ToF, ventricular septal defect with aortic dextroposition and isolated peripheral pulmonic stenosis (PPS). All forms of ToF were represented, including variants with pulmonic stenosis, pulmonic atresia and absent pulmonary valve. No individual within this family met diagnostic criteria for any previously described clinical syndrome, including Alagille syndrome (AGS), caused by haploinsufficiency for **jagged1**. All mutation carriers had characteristic but variable facial features, including long, narrow and upslanting palpebral fissures, prominent nasal bridge, square dental arch and broad, prominent chin. This appearance was distinct from that of unaffected family members and typical AGS patients. The glycine corresponding to position 274 is highly conserved in other **epidermal** growth factor-like domains of **jagged1** and in those of other proteins. Its substitution in other proteins has been associated with mild or atypical variants of disease. These data support either a relative loss-of-function or a gain-of-function pathogenetic mechanism in this family and suggest that **JAG1** mutations may contribute significantly to common variants of right heart obstructive disease.

L3 ANSWER 44 OF 76 MEDLINE on STN DUPLICATE 24

TI The mouse slalom mutant demonstrates a role for **Jagged1** in

neuroepithelial patterning in the organ of Corti.
AU Tsai H; Hardisty R E; Rhodes C; Kiernan A E; Roby P; Tymowska-Lalanne Z; Mburu P; Rastan S; Hunter A J; Brown S D; Steel K P
SO HUMAN MOLECULAR GENETICS, (2001 Mar 1) 10 (5) 507-12.
Journal code: 9208958. ISSN: 0964-6906.
AB The Notch signalling pathway has recently been implicated in the development and patterning of the sensory **epithelium** in the cochlea, the organ of Corti. As part of an ongoing large-scale mutagenesis programme to identify new deaf or vestibular mouse mutants, we have identified a novel mouse mutant, slalom, which shows abnormalities in the patterning of hair cells in the organ of Corti and missing ampullae, structures that house the sensory **epithelia** of the semicircular canals. We show that the slalom mutant carries a mutation in the **Jagged1** gene, implicating a new ligand in the signalling processes that pattern the inner ear neuro-**epithelium**.

L3 ANSWER 28 OF 76 MEDLINE on STN DUPLICATE 16
TI Familial deafness, congenital heart defects, and posterior embryotoxon caused by cysteine substitution in the first **epidermal** -growth-factor-like domain of **jagged 1**.
AU Le Caignec C; Lefevre M; Schott J J; Chaventre A; Gayet M; Calais C; Moisan J P
SO AMERICAN JOURNAL OF HUMAN GENETICS, (2002 Jul) 71 (1) 180-6.
Journal code: 0370475. ISSN: 0002-9297.
AB In the present study, we report a kindred with hearing loss, congenital heart defects, and posterior embryotoxon, segregating as autosomal dominant traits. Six of seven available affected patients manifested mild-to-severe combined hearing loss, predominantly affecting middle frequencies. Two patients were diagnosed with vestibular pathology. All patients had congenital heart defects, including tetralogy of Fallot, ventricular septal defect, or isolated peripheral pulmonic stenosis. No individual in this family met diagnostic criteria for any previously described clinical syndrome. A candidate-gene approach was undertaken and culminated in the identification of a novel **Jagged 1** (**JAG1**) missense mutation (C234Y) in the first cysteine of the first **epidermal**-growth-factor-like repeat domain of the protein. **JAG1** is a cell-surface ligand in the Notch signaling pathway. Mutations in **JAG1** have been identified in patients with Alagille syndrome. Our findings revealed a unique phenotype with highly penetrant deafness, posterior embryotoxon, and congenital heart defects but with variable expressivity in a large kindred, which demonstrates that mutation in **JAG1** can cause hearing loss.

L3 ANSWER 18 OF 76 MEDLINE on STN
TI The Notch ligand **Jagged-1** is able to induce maturation of monocyte-derived human dendritic cells.
AU Weijzen Sanne; Velders Markwin P; Elmishad Amira G; Bacon Patricia E; Panella Jeffrey R; Nickoloff Brian J; Miele Lucio; Kast W Martin
SO JOURNAL OF IMMUNOLOGY, (2002 Oct 15) 169 (8) 4273-8.
Journal code: 2985117R. ISSN: 0022-1767.
AB Notch receptors play a key role in several cellular processes including differentiation, proliferation, and apoptosis. This study investigated whether the activation of Notch signaling would affect the maturation of dendritic cells (DCs). Direct stimulation of Notch signaling in DCs with a peptide ligand induced DC maturation, similar to LPS: DCs up-regulated maturation markers, produced IL-12, lost endocytosis capacity, and became able to activate allogeneic T cells. Furthermore, coculture of DCs with cells expressing Notch ligand **Jagged-1** induced up-regulation of maturation markers, IL-12 production, T cell proliferative responses, and IFN-gamma production. Our data suggest that activation of Notch by **Jagged-1** plays an important role in maturation of human DCs. Additionally, they reveal a novel role

for Notch signaling in cell maturation events distal to the cell fate decision fork. These data may have important medical implications, since they provide new reagents to induce DC activity, which may be beneficial as adjuvants in situations where an immune response needs to be elicited, such as tumor immunotherapy.

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